METHOD AND SYSTEM TO INVESTIGATE A COMPLEX CHEMICAL SPACE

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BACKGROUND OF THE INVENTION

[0001] The present invention relates to a combinatorial high throughput screening method and system.

[0002] Combinatorial organic synthesis (COS) is a high throughput screening method that was developed for pharmaceuticals. COS uses systematic and repetitive synthesis to produce diverse molecular entities formed from sets of chemical "building blocks." As with traditional research, COS relies on experimental synthesis methodology. However instead of synthesizing a single compound, COS exploits automation and miniaturization to produce large libraries of compounds through successive stages, each of which produces a chemical modification of an existing molecule of a preceding stage. Libraries are physical, trackable collections of samples resulting from a definable set of the COS process or reaction steps. The libraries comprise compounds that can be screened for various activities.

[0003] Combinatorial high throughput screening (CHTS) is an HTS method that incorporates characteristics of COS. The CHTS methodology is marked by the search for high order synergies and effects of complex combinations of experimental variables through the use of large arrays in which multiple factors can be varied through multiple levels. Factors of an experiment can be varied within an array (typically formulation variables) and between an array and a condition (both formulation and processing variables). Results from the CHTS experiment can be used to compare properties of the products in order to discover "leads" – formulations and/or processing conditions that indicate commercial potential.

[0004] The steps of a CHTS methodology can be broken down into generic operations including selecting chemicals to be used in an experiment; introducing the chemicals into a formulation system (typically by weighing and dissolving to form stock solutions), combining aliquots of the solutions into formulations or mixtures in a geometrical array (typically by the use of a pipetting robot); processing the array of chemical combinations into products; and evaluating the products to produce results.

[0005] Typically, CHTS methodology is characterized by parallel reactions at a micro scale. In one aspect, CHTS can be described as a method comprising (A) an iteration of steps of (i) selecting a set of reactants; (ii) reacting the set and (iii) evaluating a set of products of the reacting step and (B) repeating the iteration of steps (i), (ii) and (iii) wherein a successive set of reactants selected for a step (i) is chosen as a result of an evaluating step (iii) of a preceding iteration.

[0006] Results from an experiment can be evaluated by aid of mathematical models as taught by G.E.P. Box and N. R. Draper, Empirical Model-Building and Response Surfaces, John Wiley and Sons, NY, 1987, p 20-22. The models can be used to find an approximation, typically a polynomial, to an unknown underlying theoretical function. For example, Taylor's Series expansion is a polynomial that can provide a valuable approximation of first or second order experimental interactions.

[0007] However, the study of catalyzed chemical reactions by CHTS involves the investigation of a complex experimental space characterized by multiple qualitative and quantitative factor levels. Typically, the interactions of a catalyzed chemical reaction such as a carbonylation reaction can involve interactions of an order of 6 or 9 or greater. While Taylor expansion approximation can be effectively applied to analyze first or second order interactions, it is useless to study CHTS results from a complex catalyzed chemical reaction.

[0008] Another problem is that catalyzed chemical reactions can be unpredictable. Well-known protocols in one area of chemistry cannot be applied to another area with assurance of success. For example, U.S. Pat. 6143914 shows that

some combinations of various metals unexpectedly increase a carbonylation catalyst turnover number (TON) and other related combinations do not. "Due to the complicated mechanistic nature of many transition metal based catalysts, structure - activity relationships are often unpredictable, leaving empirical exploration and serendipity the most common routes to discovery." J. Tian & G. W. Coates, Angew. Chem Int. Ed. 2000, 39, p 3626. This high degree of irregularity and unpredictability is illustrated in FIG.1.

[0009] There is a need for a methodology to examine the complex higher order and unpredictable interactions of a CHTS catalyzed chemical reaction experiment that cannot be examined by Taylor Series expansion or other standard methodology.

BRIEF SUMMARY OF THE INVENTION

[0010] The invention provides a particularly well-suited experimental methodology to investigate multiple and complex interactions of a catalyzed chemical reaction that involves both qualitative and quantitative factor levels. According to the invention, an experimental space of a catalyzed chemical reaction is defined to represent at least three factor interactions, a CHTS method is effected on the catalyzed chemical experimental space to produce results and results are analyzed according to matrix algebra to select a best case set of factor levels from the catalyzed experimental space.

[0011] In another embodiment, a CHTS experiment is conducted on a complex experimental space comprising qualitative and quantitative factors to produce first data results, (B) the first data results are analyzed according to matrix algebra, (C) a standard deviation of the analyzed results is defined, (D) data results that positively exceed the standard deviation are selected, (E) a next experimental space is defined according to the selected data results and (F) steps (A) through (E) are reiterated on the next experimental space until data results selected in step (D) represent satisfactory leads.

[0012] In yet another embodiment, a system for investigating a catalyzed experimental space, comprises a reactor for effecting a CHTS method on the catalyzed chemical experimental space to produce results and a programmed controller to analyze the results according to matrix algebra to select a best case set of factor levels from the catalyzed experimental space.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 is a graphic representation of a complex catalyzed chemical experimental space;

[0014] FIG. 2 is a schematic representation of a CHTS system;

[0015] FIG. 3 shows representations of vector matrix forms; and

[00‘6] FIG. 4 is a normal probability plot.

DETAILED DESCRIPTION OF THE INVENTION

[0017] A purpose of a CHTS experiment is to locate anomalies that represent high-value "leads." Leads are results that identify candidate factors and levels for a commercial process. According to the invention, matrix algebra is combined with CHTS to examine the very high-level interactions of a chemical catalytic reaction. In the CHTS/matrix algebra approach, a CHTS experiment in many factors can be run and then modeled to generate <u>all</u> main, 2^{nd}, 3^{rd}, 4^{th} and even higher interactions. Suitably, the results can be represented according to a general linear model (GLM). A statistical analysis of the represented results determines high-order interaction leads.

[0018] In a typical CHTS method, a multiplicity of tagged reactants is subjected to an iteration of steps of (A) (i) simultaneously reacting the reactants, (ii) identifying a multiplicity of tagged products of the reaction and (B) evaluating the identified products after completion of a single or repeated iteration (A). A typical CHTS can utilize advanced automated, robotic, computerized and controlled loading, reacting and evaluating procedures.

[0019] The results from the CHTS experiment are analyzed using matrix algebra to extract combinations of the experiment interactions. A mathematical matrix is a representation of real numbers in a rectangular array. Matrices are important tools for expressing and discussing problems that may involve complex data sets. Matrix analysis is a multivariant methodology for expressing and manipulating these kinds of data and for solving problems posed by the data. Matrix operations can include representation (posing or modeling data in a matrix representation), addition, subtraction, scalar multiplication, matrix multiplication, multiplication by inverse, transposition (interchanging rows and columns) and distribution (assigning a probability value). Matrices can be manipulated to produce a sum, difference, scalar multiple, matrix multiple, product or transpose.

[0020] In the present invention, the matrices are representations of CHTS results in a rectangular array. The runs from the CHTS experiment provide sets of results or y's, one for each run, each correlated with a set of levels of factors, x_t. Each run y is associated with an error e. Each of the factors or interactions is associated with a coefficient β. These elements (x's, their interactions and y's) can be represented in vector/matrix form as shown in FIG. 3, wherein levels of factors and interactions form a rectangular array or matrix (20) of scalar values X. Further in FIG. 3, y's, β's and e's are represented in single column matrices (10), (30), and (40). A matrix estimation equation of the system can be as follows:

$$y = X\beta + e \qquad \text{(I)}$$

[0021] where X is a matrix of factor and interaction levels in the experiment, y is a matrix of experimental results, β is effects (both main effects and interaction effects), every e_i in e has the same variance σ^2, error terms e_i arise from a normal distribution and expected value E(y) (definition: the value of the response if no error is present) of the response is $E(y) = X\beta$.

[0022] The method involves solving the above matrix estimation equation (I), according to the relationship:

$$\beta = (X'X)^{-1}X'y \qquad \text{(II)}$$

[0023] where superscript ' indicates a transpose of a matrix (in which each row becomes a column and each column a row). The superscript $^{-1}$ indicates an inverse function of a matrix. Thus for any square matrix A, a relation can be defined as $AA^{-1} = I$, where I is the identity matrix 50 shown in the FIG. 3 model.

[0024] Accordingly, results can be assembled as an n x 1 vector y and factor level values can be assembled into an n x k+1 matrix X with 1's as designations in a first column and each other column containing the coded factor level values (+1's and −1's representing the extents of the values of the factors and interactions). Matrix equation (I) is then solved for effects parameters β.

[0025] The effects parameters of matrix β are then examined for statistical significance. The null hypothesis can be applied in this examination. The null hypothesis is that all of the effects observed in the experiment are caused simply by random processes. If this is correct, the effects will fit to a normal distribution and form a relatively straight line in a probability plot. In FIG. 4; E100 is a straight line representing a results approximation. The line is flanked by dashed lines denoting multiples of standard deviations. A desired standard deviation can be selected by an experimenter for the experiment. Any effects that fall off the line by more than the standard deviation can be interpreted to have been caused by nonrandom processes, as taught by D. Montgomery, Design and Analysis of Experiments, 3rd Ed., John Wiley, 1991, NY, p 99. Effects that positively exceed the deviation can represent combinations that are failures or combinations that provide synergistic improvement, i.e., leads.

[0026] In a preferred embodiment, results from the CHTS method are analyzed by matrix algebra by steps of (A) representing the results as an n x 1 matrix y where n = a number of factor level combinations in the experiment, (B) representing extents of the factor level combinations in an n x n matrix X, (C) solving n

simultaneous equations represented by the matrices according to matrix algebra to form a results matrix β and (D) examining the results matrix β to identify effects outside a standard deviation.

[0027] The step (B) can comprise coding extents of the factor level combinations as a +1 or –1 and representing the coded extents as the n x 1 matrix y. The step (C) can comprise (i) transposing matrix X to form matrix X', (ii) postmultiplying X' by X to generate a matrix and (iii) postmultiplying the generated matrix by y to form the results matrix β. The step (D) can comprise (i) representing the results matrix β as a normal probability plot, defining a standard deviation for results of the plot and (iii) identifying positive interactions outside of the standard deviation. The standard deviation can represent a probability that a result deviation from the standard is random and that positive interactions can be identified outside of the deviation. In one embodiment, the probability can be established at 95 percent or better to define an experimental space for a commercial process or the probability can be established at 99.7 percent or better to define a best set of factor levels as leads for a commercial process.

[0028] I n one embodiment, the invention is applied to screen for a catalyst to prepare a diaryl carbonate by carbonylation. Diaryl carbonates such as diphenyl carbonate can be prepared by reaction of hydroxyaromatic compounds such as phenol with oxygen and carbon monoxide in the presence of a catalyst composition comprising a Group VIIIB metal such as palladium or a compound thereof, a bromide source such as a quaternary ammonium or hexaalkylguanidinium bromide and a polyaniline in partially oxidized and partially reduced form.

[0029] Various methods for the preparation of diaryl carbonates by a carbonylation reaction of hydroxyaromatic compounds with carbon monoxide and oxygen have been disclosed. The carbonylation reaction requires a rather complex catalyst. Reference is made, for example, to Chaudhari et al., U.S. Pat. 5,917,077. The catalyst compositions described therein comprise a Group VIIIB metal (i.e., a

metal selected from the group consisting of ruthenium, rhodium, palladium, osmium, iridium and platinum) or a complex thereof.

[0030] The catalyst material also includes a bromide source. This may be a quaternary ammonium or quaternary phosphonium bromide or a hexaalkylguanidinium bromide. The guanidinium salts are often preferred; they include the ∀, T-bis(pentaalkylguanidinium)alkane salts. Salts in which the alkyl groups contain 2-6 carbon atoms and especially tetra-n-butylammonium bromide and hexaethylguanidinium bromide are particularly preferred.

[0031] Other catalytic constituents are necessary in accordance with Chaudhari et al. The constituents include inorganic cocatalysts, typically complexes of cobalt(II) salts with organic compounds capable of forming complexes, especially pentadentate complexes. Illustrative organic compounds of this type are nitrogen-heterocyclic compounds including pyridines, bipyridines, terpyridines, quinolines, isoquinolines and biquinolines; aliphatic polyamines such as ethylenediamine and tetraalkylethylenediamines; crown ethers; aromatic or aliphatic amine ethers such as cryptanes; and Schiff bases. The especially preferred inorganic cocatalyst in many instances is a cobalt(II) complex with bis-3-(salicylalamino)propylmethylamine.

[0032] Organic cocatalysts may be present. These cocatalysts include various terpyridine, phenanthroline, quinoline and isoquinoline compounds including 2,2':6',2"-terpyridine, 4-methylthio-2,2':6',2"-terpyridine and 2,2':6',2"-terpyridine N-oxide,1,10-phenanthroline, 2,4,7,8-tetramethyl-1,10-phenanthroline, 4,7-diphenyl-1,10, phenanthroline and 3,4,7,8-tetramethy-1,10-phenanthroline. The terpyridines and especially 2,2':6',2"-terpyridine are preferred.

[0033] Another catalyst constituent is a polyaniline in partially oxidized and partially reduced form.

[0034] Any hydroxyaromatic compound may be employed. Monohydroxyaromatic compounds, such as phenol, the cresols, the xylenols and p-cumylphenol are preferred with phenol being most preferred. The method may be

employed with dihydroxyaromatic compounds such as resorcinol, hydroquinone and 2,2-bis(4-hydroxyphenyl)propane or "bisphenol A," whereupon the products are polycarbonates.

[0035] Other reagents in the carbonylation process are oxygen and carbon monoxide, which react with the phenol to form the desired diaryl carbonate.

[0036] These and other features will become apparent from FIG. 2 and the following detailed discussion, which by way of example without limitation describe preferred embodiments of the present invention.

[0037] FIG. 2 is a schematic representation of a system 10 for CHTS according to the invention. FIG. 2 shows system 10 including dispensing assembly 12, reactor 14, detector 16 and controller 18. Further shown, is X-Y-Z robotic positioning stage 20, which supports array plate 22 with wells 24. The dispensing assembly 12 includes a battery of pipettes 26 that are controlled by controller 18. X-Y-Z robotic positioning stage 20 is controlled by controller 18 to position wells 24 of the array plate 22 beneath displacement pipettes 26 for delivery of test solutions from reservoirs 28.

[0038] Controller 18 controls aspiration of precursor solution into the battery of pipettes 26 and sequential positioning of the wells 24 of array plate 22 so that a prescribed stoichiometry and/or composition of reactant and/or catalyst can be delivered to the wells 24. By coordinating activation of the pipettes 26 and movement of plate 22 on the robotic X-Y-Z stage 20, a library of materials can be generated in a two-dimensional array for use in the CHTS method. Also, the controller 18 can be used to control sequence of charging of sample to reactor 14 and to control operation of the reactor 14 and the detector 16. Controller 18 can be a computer, processor, microprocessor or the like.

[0039] An experimental space definition defines the contents of the wells 24 for the CHTS method. The space can be defined according to any design that results in a representation of at least three factor interactions. Suitable designs include

fractional factorial design, Latin square design, Plackett-Burman design or Taguchi design. Preferably the design results in a representation of all interactions and preferably, the design is an orthogonal design such as a full factorial design. The design can be embodied as an algorithm or program resident in controller 18.

[0040] Controller 18 controls the sequence of charging array plate 22 into the reactor 14, which is synchronized with operation of detector 16. Detector 16 detects products of reaction in the wells 24 of an array plate 22 after reaction in reactor 14. Detector 16 can utilize chromotography, infra red spectroscopy, mass spectroscopy, laser mass spectroscopy, microspectroscopy, NMR or the like to determine the constituency of each reaction product. The controller 18 uses data on the sample charged by the pipettes 26 and on the constituency of reaction product for each sample from detector 16 to correlate a detected product with at least one varying parameter of reaction. Additionally, an algorithm or program can be resident in the controller 18 to represent the CHTS results according to a matrix form and to analyze the represented results by matrix algebra to determine leads.

[0041] As an example, if the method and system of FIG.1 is applied to study a carbonylation catalyst and/or to determine optimum carbonylation reaction conditions, the detector 16 analyzes the contents of the well for carbonylated product. In this case, the detector 16 can use Raman spectroscopy. The Raman peak is integrated using the analyzer electronics and the resulting data can be stored in the controller 18. Other analytical methods may be used - for example, Infrared spectrometry, mass spectrometry, headspace gas-liquid chromatography and fluorescence detection.

[0042] A method of screening complex catalyzed chemical reactions can be conducted in the FIG. 2 system 10. According to the method, catalyzed formulations are prepared according to any suitable procedure. For example, one procedure produces a homogeneous chemical reaction utilizing multiphase reactant systems. In this procedure, a formulation is prepared that represents a first reactant system that is at least partially embodied in a liquid. Each formulation is loaded as a thin film to a respective well 24 of the array plate 22 and the plate 22 is charged into reactor 14.

During the subsequent reaction, the liquid of the first reactant system embodied is contacted with a second reactant system at least partially embodied in a gas. The liquid forms a film having a thickness sufficient to allow the reaction rate of the reaction to be essentially independent of the mass transfer rate of the second reactant system into the liquid.

[0043] The method herein described can be used with any suitable catalyzed chemical reactant system. For example, the system and method herein can be used for determining a method for producing diphenyl carbonate (DPC). Diphenyl carbonate (DPC) is useful, inter alia, as an intermediate in the preparation of polycarbonates. One method for producing DPC involves the carbonylation of a hydroxyaromatic compound (e.g., phenol) in the presence of a catalyst system. A carbonylation catalyst system typically includes a Group VIII B metal (e.g., palladium), a halide composition and a combination of inorganic co-catalysts (IOCCs).

[0044] Generally, testing of new catalyst systems has been accomplished at macro-scale and, because the mechanism of this carbonylation reaction is not fully understood, the identity of additional effective IOCCs has eluded practitioners. An embodiment of the present invention allows a homogeneous carbonylation reaction to be carried out in parallel with various potential catalyst systems and, consequently, this embodiment can be used to identify effective IOCCs for the carbonylation of phenol.

[0045] The following Example is illustrative and should not be construed as a limitation on the scope of the claims unless a limitation is specifically recited.

EXAMPLE

[0046] This EXAMPLE illustrates an identification of an active and selective catalyst for the production of aromatic carbonates. The procedure identifies the best catalyst from a complex chemical space, where the chemical space is defined as an assemblage of all possible experimental conditions defined by a set of variable

parameters such as formulation ingredient identity or amount or process parameter such as reaction time, temperature, or pressure.

[0047] The chemical space consists of the following TABLE 1 chemical factor levels and TABLE 2 processing factor levels:

TABLE 1

Factor	Level	Level
Primary Catalyst	Ru(acac)3 Pt(acac)2	All at 25 ppm
Metal Cocatalyst	Mn(acac)2 Fe(acac)3	150 and 1500 ppm
Cosolvent	Dimethylformamide (DMFA), Tetrahydrofuran (THF)	All at 10%
Anion Cocatalyst	Cl^-, Br^-, (as hexamethylguanadinium salts)	All at 5000 ppm

TABLE 2

Factor	Level
Pressure	1000 psi, 1500 psi (8% Oxygen in Carbon Monoxide)
Temperature	100 C, 120 C

[0048] The system has seven factors, each at two levels. There are $2^7 = 128$ possible combinations of these levels. The experiment is set up according to a full factorial design with 128 runs as shown in TABLE 3. In the experiment, catalyzed mixtures are made up in phenol solvent using the concentrations of each component as given in the rows of TABLE 3. The total volume of each catalyzed mixture is 1.0 ml. From each mixture, a 25 microliter aliquot is dispensed into a 2 ml reaction vial, forming a film on the bottom. The vials are grouped in array plates by process conditions (as specified in the Pressure and Temperature columns in the table) and each array plate is loaded into a high pressure autoclave and subjected to the reaction conditions specified. At the end of the reaction time, the reactor is cooled and depressurized and the contents of each vial are analyzed for diphenyl carbonate

product using a gas chromatographic method. A turnover number (TON) for each reaction is calculated as mols of diphenylcarbonate/mols of primary catalyst. The results are given in the TON column of TABLE 3.

TABLE 3

A: Primary Catalyst	B: Metal Cocatalyst	C: Metal Cocatalyst Amount	D: Cosolvent	E: Anion Cocatalyst	F: Pressure	G: Temp.	TON
Pt	Mn	150	DMFA	Br	1000	100	3340
Ru	Mn	150	DMFA	Br	1000	100	3470
Pt	Fe	150	DMFA	Br	1000	100	2360
Ru	Fe	150	DMFA	Br	1000	100	2260
Pt	Mn	1500	DMFA	Br	1000	100	2310
Ru	Mn	1500	DMFA	Br	1000	100	2060
Pt	Fe	1500	DMFA	Br	1000	100	3030
Ru	Fe	1500	DMFA	Br	1000	100	3200
Pt	Mn	150	THF	Br	1000	100	2430
Ru	Mn	150	THF	Br	1000	100	2270
Pt	Fe	150	THF	Br	1000	100	2910
Ru	Fe	150	THF	Br	1000	100	3160
Pt	Mn	1500	THF	Br	1000	100	3270
Ru	Mn	1500	THF	Br	1000	100	3030
Pt	Fe	1500	THF	Br	1000	100	2260
Ru	Fe	1500	THF	Br	1000	100	2470
Pt	Mn	150	DMFA	Cl	1000	100	3040
Ru	Mn	150	DMFA	Cl	1000	100	3340
Pt	Fe	150	DMFA	Cl	1000	100	2030
Ru	Fe	150	DMFA	Cl	1000	100	1860
Pt	Mn	1500	DMFA	Cl	1000	100	2200
Ru	Mn	1500	DMFA	Cl	1000	100	1920
Pt	Fe	1500	DMFA	Cl	1000	100	3290
Ru	Fe	1500	DMFA	Cl	1000	100	2910
Pt	Mn	150	THF	Cl	1000	100	2260
Ru	Mn	150	THF	Cl	1000	100	2410
Pt	Fe	150	THF	Cl	1000	100	3260
Ru	Fe	150	THF	Cl	1000	100	3200
Pt	Mn	1500	THF	Cl	1000	100	3360
Ru	Mn	1500	THF	Cl	1000	100	3090
Pt	Fe	1500	THF	Cl	1000	100	2320
Ru	Fe	1500	THF	Cl	1000	100	2320
Pt	Mn	150	DMFA	Br	1500	100	3230
Ru	Mn	150	DMFA	Br	1500	100	3710
Pt	Fe	150	DMFA	Br	1500	100	2140
Ru	Fe	150	DMFA	Br	1500	100	2500
Pt	Mn	1500	DMFA	Br	1500	100	2490
Ru	Mn	1500	DMFA	Br	1500	100	2230
Pt	Fe	1500	DMFA	Br	1500	100	3070

Ru	Fe	1500	DMFA	Br	1500	100	3360
Pt	Mn	150	THF	Br	1500	100	2680
Ru	Mn	150	THF	Br	1500	100	2640
Pt	Fe	150	THF	Br	1500	100	3520
Ru	Fe	150	THF	Br	1500	100	3620
Pt	Mn	1500	THF	Br	1500	100	3620
Ru	Mn	1500	THF	Br	1500	100	3830
Pt	Fe	1500	THF	Br	1500	100	2710
Ru	Fe	1500	THF	Br	1500	100	2580
Pt	Mn	150	DMFA	Cl	1500	100	3310
Ru	Mn	150	DMFA	Cl	1500	100	3740
Pt	Fe	150	DMFA	Cl	1500	100	2460
Ru	Fe	150	DMFA	Cl	1500	100	2410
Pt	Mn	1500	DMFA	Cl	1500	100	2020
Ru	Mn	1500	DMFA	Cl	1500	100	2300
Pt	Fe	1500	DMFA	Cl	1500	100	3270
Ru	Fe	1500	DMFA	Cl	1500	100	3250
Pt	Mn	150	THF	Cl	1500	100	2800
Ru	Mn	150	THF	Cl	1500	100	2520
Pt	Fe	150	THF	Cl	1500	100	3850
Ru	Fe	150	THF	Cl	1500	100	3570
Pt	Mn	1500	THF	Cl	1500	100	3540
Ru	Mn	1500	THF	Cl	1500	100	3950
Pt	Fe	1500	THF	Cl	1500	100	2730
Ru	Fe	1500	THF	Cl	1500	100	2520
Pt	Mn	150	DMFA	Br	1000	120	3300
Ru	Mn	150	DMFA	Br	1000	120	3800
Pt	Fe	150	DMFA	Br	1000	120	2640
Ru	Fe	150	DMFA	Br	1000	120	2520
Pt	Mn	1500	DMFA	Br	1000	120	2220
Ru	Mn	1500	DMFA	Br	1000	120	2270
Pt	Fe	1500	DMFA	Br	1000	120	3960
Ru	Fe	1500	DMFA	Br	1000	120	3360
Pt	Mn	150	THF	Br	1000	120	2560
Ru	Mn	150	THF	Br	1000	120	2440
Pt	Fe	150	THF	Br	1000	120	3560
Ru	Fe	150	THF	Br	1000	120	3620
Pt	Mn	1500	THF	Br	1000	120	3650
Ru	Mn	1500	THF	Br	1000	120	3570
Pt	Fe	1500	THF	Br	1000	120	2650
Ru	Fe	1500	THF	Br	1000	120	2710
Pt	Mn	150	DMFA	Cl	1000	120	3380
Ru	Mn	150	DMFA	Cl	1000	120	3430
Pt	Fe	150	DMFA	Cl	1000	120	2480
Ru	Fe	150	DMFA	Cl	1000	120	2310
Pt	Mn	1500	DMFA	Cl	1000	120	2510

Ru	Mn	1500	DMFA	Cl	1000	120	2410
Pt	Fe	1500	DMFA	Cl	1000	120	3320
Ru	Fe	1500	DMFA	Cl	1000	120	3620
Pt	Mn	150	THF	Cl	1000	120	2880
Ru	Mn	150	THF	Cl	1000	120	2430
Pt	Fe	150	THF	Cl	1000	120	3940
Ru	Fe	150	THF	Cl	1000	120	4290
Pt	Mn	1500	THF	Cl	1000	120	3730
Ru	Mn	1500	THF	Cl	1000	120	3730
Pt	Fe	1500	THF	Cl	1000	120	2730
Ru	Fe	1500	THF	Cl	1000	120	2480
Pt	Mn	150	DMFA	Br	1500	120	3510
Ru	Mn	150	DMFA	Br	1500	120	3420
Pt	Fe	150	DMFA	Br	1500	120	2340
Ru	Fe	150	DMFA	Br	1500	120	2390
Pt	Mn	1500	DMFA	Br	1500	120	2210
Ru	Mn	1500	DMFA	Br	1500	120	2660
Pt	Fe	1500	DMFA	Br	1500	120	3270
Ru	Fe	1500	DMFA	Br	1500	120	3550
Pt	Mn	150	THF	Br	1500	120	2450
Ru	Mn	150	THF	Br	1500	120	2830
Pt	Fe	150	THF	Br	1500	120	3910
Ru	Fe	150	THF	Br	1500	120	3850
Pt	Mn	1500	THF	Br	1500	120	3470
Ru	Mn	1500	THF	Br	1500	120	3730
Pt	Fe	1500	THF	Br	1500	120	2360
Ru	Fe	1500	THF	Br	1500	120	2660
Pt	Mn	150	DMFA	Cl	1500	120	3640
Ru	Mn	150	DMFA	Cl	1500	120	3440
Pt	Fe	150	DMFA	Cl	1500	120	2380
Ru	Fe	150	DMFA	Cl	1500	120	2230
Pt	Mn	1500	DMFA	Cl	1500	120	2510
Ru	Mn	1500	DMFA	Cl	1500	120	2150
Pt	Fe	1500	DMFA	Cl	1500	120	3100
Ru	Fe	1500	DMFA	Cl	1500	120	3810
Pt	Mn	150	THF	Cl	1500	120	2380
Ru	Mn	150	THF	Cl	1500	120	2900
Pt	Fe	150	THF	Cl	1500	120	3740
Ru	Fe	150	THF	Cl	1500	120	3620
Pt	Mn	1500	THF	Cl	1500	120	3610
Ru	Mn	1500	THF	Cl	1500	120	3680
Pt	Fe	1500	THF	Cl	1500	120	2570
Ru	Fe	1500	THF	Cl	1500	120	2880

[0001] Analysis of the data using matrix estimation formula (I) gives the information of TABLE 4. The Terms are the main effects and interactions of the factors in TABLE 3 and A-F are as given in the heading of TABLE 3. Thus A is the main effect of Factor "Primary Catalyst" and AD is the interaction effect of the Factors "Primary Catalyst" and "Cosolvent." Effects are β's.

Table 4

Term	Effect (β)
A	-25
B	2
C	-43
D	164
E	32
F	20
G	229
AB	10
AC	2
AD	7
AE	22
AF	-26
AG	42
BC	39
BD	29
BE	73
BF	16
BG	-12
CD	6
CE	-28
CF	23
CG	-27
DE	28
DF	-31
DG	-35
EF	-9
EG	-25
FG	-188
ABC	-21
ABD	13
ABE	-6
ABF	4
ABG	1
ACD	-14
ACE	1
ACF	27
ACG	-20
ADE	30
ADF	-17
ADG	-6
AEF	-53
AEG	17
AFG	53
BCD	-1005
BCE	-36
BCF	14
BCG	28
BDE	-10
BDF	47
BDG	7
BEF	36

Term	Effect (β)
BFG	22
CDE	-24
CDF	-14
CDG	1
CEF	-67
CEG	20
CFG	13
DEF	1
DEG	-16
DFG	40
EFG	-37
ABCD	2
ABCE	-52
ABCF	-40
ABCG	30
ABDE	44
ABDF	13
ABDG	21
ABEF	-11
ABEG	13
ABFG	20
ACDE	-4
ACDF	-22
ACDG	12
ACEF	-40
ACEG	21
ACFG	-32
ADEF	7
ADEG	-41
ADFG	-1
AEFG	4
BCDE	-56
BCDF	14
BCDG	24
BCEF	-8
BCEG	29
BCFG	6
BDEF	6
BDEG	12
BDFG	-32
BEFG	30
CDEF	19
CDEG	18
CDFG	7
CEFG	58
DEFG	-2
ABCDE	-8
ABCDF	16
ABCDG	29
ABCEF	-23
ABCEG	-34

Term	Effect (β)
ABDEF	-24
ABDEG	-7
ABDFG	-58
ABEFG	9
ACDEF	-25
ACDEG	22
ACDFG	-16
ACEFG	51
ADEFG	-6
BCDEF	3
BCDEG	21
BCDFG	-40
BCEFG	9
BDEFG	-26
CDEFG	18
ABCDEF	51
ABCDEG	1
ABCDFG	20
ABCEFG	-73
ABDEFG	-57
ACDEFG	-4
BCDEFG	4
ABCDEFG	-11

[0001] The Effects are fitted to a normal probability plot and four points are identified as falling outside two standard deviations of the straight line fit: D, G, FG, and BCD. The BCD interaction is identified as a potential lead to nonlinear behavior simultaneously involving the Cocatalyst Metal (B), the Cocatalyst Metal Amount (C),

and the Cosolvent (D). Repeated followup iterations identify a strong synergistic effect of high levels of Fe in the presence of THF.

[0001] While preferred embodiments of the invention have been described, the present invention is capable of variation and modification and therefore should not be limited to the precise details of the EXAMPLE. The invention includes changes and alterations that fall within the purview of the following claims.